DEPARTMENT OF CHEMISTRY AND ENVIRONMENTAL SCIENCE
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DATE: WEDNESDAY, JANUARY 31, 2018

WHERE: KUPFRIAN Lecture hall 118
TIME: 1:00PM

GUEST SPEAKER

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TOPIC

Chemically Engineered Peptides as Synthetic Tools for Modulation of Biological Functions

ABSTRACT

Myeloid cell leukemia 1 (Mcl-1) has emerged as one of the top ten most widely expressed pathologic factors in human cancer and neutralizing this antiapoptotic protein has become a clear priority for apoptosis research. Short peptides that mimic helical BH3 domains are ideal ligands for selective targeting of Mcl-1 and modulation of its biological functions.

However, in vivo efficacy of short peptides is compromised by their loss of secondary structure, susceptibility to proteolytic degradation, and difficulty in penetrating intact cell membranes.[1,2] Preliminary studies indicate that a strategy of stabilizing Mcl-1- targeting peptides by crosslinking them with covalent hydrocarbon "staples" can confer significantly improved affinity for anti-apoptotic receptors. However, cross-linking does not uniformly improve peptide helicity and binding, and iterative optimization involving extensive mutagenesis is typically required to achieve potent and selective stapled peptide inhibitors. The virtually unlimited structural variations within this design scheme present a challenge with respect to identifying the best-binding modified peptide(s).

To address this problem, we applied synthetic libraries, which enable the synthesis and screening of chemically modified repertoires of peptidic scaffolds containing non-native modules that can be assayed using high-throughput screening for binding. By applying this method, improved molecules with low-nanomolar binding affinity for Mcl-1 and high selectivity over other Bcl-2 paralogs were identified. Interestingly, peptides discovered in our screen contained surprising substitutions at sites that are conserved in natural binding partners.[3]

We have further optimized the stapled peptides for delivery into living cells, yielding unique cross- linked peptides that bind tightly and specifically to Mcl-1 with high protease resistance and good cell permeability.[4] Functional characterization of stapled Bim-based

BH3 peptides has led to the discovery of a new hydrocarbon staple position that provides specificity for binding to Mcl-1. We further assessed and validated the killing mechanism of lead Mcl-1 inhibitors in Mcl-1 dependent cell lines.

Reference

[1] L. D. Walensky, A. L. Kung, I. Escher, T. J. Malia, S. Barbuto, R. D. Wright, G. Wagner, G. L. Verdine, S. J. Korsmeyer, *Science* **2004**, *305*, 1466–1470.

[2] R. Rezaei Araghi, A. E. Keating, *Curr. Opin. Struct. Biol.* **2016**, *39*, 27–38.

[3] R. Rezaei Araghi, J. A. Ryan, A. Letai, A. E. Keating, *ACS Chem. Biol.* **2016**, *11*, 1238–1244.

[4] R. Rezaei Araghi, G. H. Bird, J. A. Ryan, J. Jenson, M. Godes, R. Granta, A. Letai, W. Loren, K. A. E., *Proc. Natl. Acad. Sci.* **2018**, DOI /10.1073/pnas.1712952115

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